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EXAMINER	
WESSENDORF, T	
ART UNIT	**PAPER NUMBER**
1627	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/293,670	Fisher et al
Examiner	**Art Unit**
T. Wessendorf	1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 4/24/01

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-16 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-16 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119( ).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

The request filed on 4/24/01 for a Continued Prosecution Application (CPA) under 37 CAR 1.53(d) based on parent Application No. 09/293,670 is acceptable and a CPA has been established. An action on the CPA follows.

The objection to the finality of the last Office action set forth at page 4 of the instant REMARKS has been addressed in the letter of Paper #18 stating the reason why the finality of the last Office action is proper.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-16 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The specification does not provide a specific utility for the bioactive agent identified by the instant method. The specification merely recites for a method of screening for a candidate bioactive agent that affects a population of cells but fails to recite a use for a bioactive agent isolated and identified by said screening process. A method of screening is not a utility until the method produces a utility for a given product. The instant application does not disclose the biological

role or significance of an isolated bioactive agent and more importantly, the identity of the bioactive agents from a given library that affects a population of cells. Even an intended use for the bioactive agent has not provided in the specification. It seems that the disclosure needs further research such that a specific and substantial credible utility might be found for the claimed isolated agent from a library that affects a cell population and identified by at least 3 parameters of FACS. This further research, however, is part of the act of invention and until it has been undertaken, applicant's claimed invention is incomplete.

The court in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966),expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is

> insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to a method that screens from a library an alleged agent that is bioactive but is of as yet of undetermined structure and function or biological significance that affects a population of cells as identified by measuring 3 parameters by FACS. There was no immediately apparent or "real world" utility as of the filing date.

Claims 1-16 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

See the rejection under 101, above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 3 recitation of screening a population of altered cellular phenotype by a candidate bioactive agent is not supported in the as-filed specification. Applicants rely on page 8, lines 12-18 as support. A review of said page reveal for detection of alterations in cell phenotypes i.e., different cell morphology using a FACS machine or screening for a modulators of cell phenotype. The original specification appears to claim different methods i.e., either cell phenotype alteration or modulators of cell phenotypes.

Likewise, "different candidate agent" (claim 15) and "approximately simultaneously" are not supported in the as-filed specification. Page 32, lines 6-7, for example, is relied upon. The cited page does not recite for these newly presented limitations.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method so specific for the p21 as the bioactive agent that modulates a specific tumor cell, does not reasonably provide enablement for a method using a library of any bioactive agents or nucleic acid that encodes said bioactive agents that modulates any population of cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons advanced at pages 6-9 of the last Office action, 10/6/99.

The response in the last Office action is incorporated herein. Applicants argue that if a single candidate agent is capable of altering the cellular phenotype were combined with a population of cells and sorted as claimed, such candidate agent would have been screened for and identified without a library of candidate agents. However, the specification does not teach how said agent is selected or consider to be a candidate i.e., the source by which an agent can be obtained to be classed as candidate. It would therefore take an undue amount of experimentation to determine the source by which an agent is obtained and to test each and every possible bioactive agents

that is a candidate that has the capability of making cell alterations. Furthermore, the claims recite for an altered population of cells that are being screened and not a bioactive agent that has an effect on the cell. Applicants argue that the candidate agent cannot be limiting as a list appears at page 16, lines 8-10. A mere list of compounds do not provide enablement, especially when the compounds in the list are broad as claimed. For example, there is no description as to what is considered a small organic molecules and compounds defined by the macromolecule, proteins, polynucleotide, polysaccharide (in natural or synthetic form) or to the modified forms of said biomolecules and/or combinations of these different compounds. The list covers all conceivable compounds from a simple purine to as complex as the biomolecules. To select and determine the particular agent that has the claimed capability is like looking for a needle in a haystack as there is no discriminating characteristics of the bioactive agent's effect on a population of cells. It is argued that a feature of the claimed methods is the use of multiple cellular parameters to screen for a bioactive agent capable of altering cellular phenotype. (Claims 1 and 3 do not contain this limitation). However, before measurement of even a single effect is achieved, one has to identify the cause

(agent) that causes said parameter effect. Obviously, even without an agent a population of cell in of itself can be screened by FACS employing at least three parameters such as optical properties of the cells, dye detection or apoptosis and other changes normally undergone by cells. Applicants argue that the examples provide evidence that many different types of cells may be assayed by the multiple cellular parameters, but fail to specifically cite any examples. Applicants argue that the examples show the effects of not one but three agents i.e., the p21, C-terminus fragment of said p21, and C-terminus mutant of the p21. This is still considered a single agent (p21) in native or in modified form(C-terminal and the mutant of p21 fragment). This is not the same as the agent being p21 and non-p21 agent e.g., erb, GH or SH3 etc. Applicants argue that "cells transfected with the nucleic acid encoding p21 or its PCNA binding fragment were shown to have altered cellular phenotype, while that transfected with the mutant fragment did not" is a simple example of positive and negative result. This is a more complex issue of positive and negative effects. The showing indicates the high unpredictable effect of even the single agent in its native state and when mutated results in a negative effect. If the results expected by applicants turned out to be

otherwise, then what directions would a skilled artisan follow that would lead to a candidate agent, as claimed? Applicants argue that a skilled artisan understands that the screening of a given library would be the same cell type under the same conditions such that the parameters that the cells face are the same except for the nucleic acid which each is transfected, and the same parameters which allow detection of cellular phenotype alteration would be used. The claims do not recite a certain cell type, hence, it is not apparent as to the conditions or even the nucleic acid that can be transfected that would affect the cells only in a desired manner. Accordingly, to determine the numerous possible combinations of each of the broadly recited parameters encompassed by the claims requires undue experimentation, and is nothing more than an invitation to experiment.
[It is suggested that applicants amend the claims to recite a method to the use of library of p21 and its mutants as the bioactive agents in tumor cell populations].

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). Claim 1 is indefinite as there seems to be no nexus between the preamble and the body of the claims. The preamble recites for screening a population of cells with an altered cellular phenotype. Step a) of the body of the claims recite for a candidate bioactive agent which appears to be the one being screened. Therefore, it is not clear as to which is being screened. Is it the candidate bioactive agent or the altered cells? It is not clear as to the basis by which a bioactive agent is considered a candidate. Cf. With claim 15. Furthermore, the preamble recites for screening while the concluding body of the claim recites for identifying an altered cell. Step b is unclear as to the cells being referred. Is it the population of unaltered or altered cells?

B). The recitation in claim 2 of "a library of candidate bioactive agents" is inconsistent with claim 1 "candidate bioactive agents".

C). Claim 4 recitation of the library as a retroviral library is inconsistent with claim 3 "library of nucleic acids that encodes a candidate bioactive agent".

D). The term "approximately" simultaneously in claim 16 is indefinite, especially in the absence of positive support as how determination is done approximately simultaneously.

Claims 1-3 and 5-6 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 12-33 and 35 of copending Application No. 09/062,330('330)for reasons of record.

Applicants' statement to hold this rejection in abeyance is noted. However, in the absence of a terminal disclaimer, the rejection is maintained.

Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5 of copending Application No.09/157,748 ('748) for reasons of record.

Applicants' statement to hold this rejection in abeyance is noted. However, in the absence of a terminal disclaimer, the rejection is maintained.

Claims 1-7 are provisionally rejected under 35 U.S.C. 103(a) as being obvious over copending Application No. 09/157,748 which

has a common inventor with the instant application for reasons advanced in the last Office action, pages 13-14.

Applicants requested to hold this rejection is abeyance. Applicants state that they are considering submitting a declartion under 132 to show that relevant disclosure in the present application is the work of the inventor in common in the two applications or filing of a CPA, thus bringing the application under the new 103© and making the rejection inoperable. However, since this has not been done, hence the rejection is maintained.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the

> differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 7-10 and 13-14 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nolan (WO 97/27212).

It is argued that the majority of the passages cited in the last Office action do not relate to the sorting of cells in a FACS machine. Attention is directed at e.g., Example 1, line 23 up to page 52, line 2 wherein the cells after washing is transferred to Fluorescent activated cell sorting (FACS)tube (the FACS machine, as claimed) for analysis which shows expression of Bcl2 from retroviral promoter that inhibits apoptosis. FACS machine are known to measure optical properties like (1) fluorescence which would indicate that the cell is (2) viable and that the agent inhibit (3) apoptosis. Accordingly, these three parameters are inherent to the prior art teachings which uses the same machine FACS, which in itself, is known to function by measuring the different optical properties including fluorescence. See page 1, lines 26-28 of the instant specification which recites the known fact that FACS is used to sort individual cells on the basis of optical properties, including fluorescence. See also page 33, lines 19-28 wherein

Nolan describes that once a cell with an altered phenotype is detected, the cell is isolated from the plurality which do not have altered phenotypes. This is done in any number of ways, as is known in the art, and will in some instances depend on the assy or screen. Suitable isolation techniques include FACS, expression of survival protein, (first parameter) induced expression of a cell surface protein or other molecule that can be rendered fluorescent or taggable for physical isolation; (second) death of cells (third) and isolation of DNA (fourth) or other cell viability indicator dyes, (fifth) etc. Example 1, page 51 uses FACS to analyze a fluoresceinated cell, expression of the cells, apoptosis inhibition, use of dye techniques as propidium iodide or other dyes such as ethidium bromide/acridine orange. Therefore, the broadly recited at least five cellular parameters is anticipated or would be obvious to combine as per the teachings of Nolan.

Claims 3, 8, 10, 14 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kamb (5,955,275)for reasons advanced in the previous Office action, paragraph bridging pages 15 and 16.

Applicants admit that Kamb teaches the use of FACS to separate cells based on the expression of a single reporter gene.

Applicants further admit that in another example, the population of cells is sorted based on expression of a reporter gene. But argue that Kamb does not disclose or suggest sorting of a population of cells in a FACS machine on the basis of at least three cellular parameters. As stated above, FACS machine are known to measure different optical properties such as cell viability including fluorescence. As stated by applicants, Kamb refers to GFP as a vital dye that refers to the fact that the GFP is expressed without killing the cell. Therefore, Kamb would have inherently measure two parameters i.e., cell viability and fluorescence. Further, the suggestion of Kamb of other modes of light emission indicates the inherent property of the FACS machine to measure other forms of light emission besides fluorescence. As correctly stated by applicants in the last REMARKS, Kamb discloses the sorting of the single expressed gene by sorting the cells based on the different cellular parameters of (1) a fluorescently labeled antibody (i.e., immunofluorescence); (2) quantifying measurement level of the expressed reporter gene (e.g., col.8, line 45 up to col. 9, line 7) and (3)the uptake of the GFP(a "vital dyes") or its emission or (4)the use of BFP. Therefore, the measurement of Kamb of at least three (3) specific cellular parameters by FACS machine

anticipates or renders obvious the combination of the different known parameters to identify cell population.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5-6 and 11-12 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Nolan or Kamb in view of Hide et al(Jrnl. of Cell Biology) for reasons advanced in the last Office action, pages 17-18.

Applicants argue that Hide does not disclose or suggest sorting cells in a FACS machine by separating cells on the basis of at least three cellular parameters and does not cure the shortcoming of Kamb or Nolan. Hide is combined with Kamb or Nolan for the claimed limitation of the cellular phenotype as exocytosis and measuring said cellular parameter to detect the forward and light scattering of cells to show the exocytosis effect of the cells. This attribute has been used to classify

populations of (mast) cells. Thus, applicants cannot attack the references individually when the rejection is based on the combination of references. One having ordinary skill in the art would have been motivated to measure another cellular parameters as light scattering by FACS when the cellular phenotype is caused by exocytosis to provide a clear or discernible effect of the cells. It is argued that no evidence has been provided to support the assertion that the combination of the known parameters measured by FACS result in a clear identification of the cells. The fact that each of these references measure the different parameters to provide a clear identification of the agent is sufficient evidence that the different combinations of measuring these different parameters would lead to a better identication of an agent affecting cell.

No claim is allowed.

Certain papers related to this application may be submitted to Art Unit 1627 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 O.G. 61 (November 16, 1993) and 1157 O.G. 94 (December 28, 1993)(see 37 C.F.R. 1.6(d)). The official fax telephone numbers of the Group are (703)308-7924. NOTE: If applicant does submit a paper by fax, the original signed copy

should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Mon. to Fri. from 8 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat Ph.D., can be reached on (703) 308-0570.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

tdw

7/13/01

T.D. WESSENDORF
PRIMARY EXAMINER